REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance.

Status of the Claims and Formal Matters

Claims 40-42, 71, 79 and 80 are currently pending in this application. Claims 78 and 81 have been cancelled without prejudice or disclaimer as to the claimed subject matter, solely to expedite prosecution of the present application. Claims 40 and 79 are amended. Support for the amendment to claim 40 appears in, e.g., the original claims and in paragraphs [0079] and [0083] of the published application U.S. 2006/0194715, and support for the amendment to claim 79 appears in, e.g., the original claims and in the paragraph [0024] of the published application. No new matter is added.

Reply to Claim Objections under 37 CFR 1.75(c)

Claim 40 is objected to under 37 CFR 1.75 (c), for allegedly containing informalities. In view of amendments to claim 40, this objection is moot and should be withdrawn.

Rejections under § 112, first paragraph

Claims 79 and 81 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. In view of cancellation to claim 81 and amendments to claim 79, this rejection is moot and should be withdrawn. Claim 79 is amended to clarify that mass spectrometry is a preferred label-free detection method. Applicants request reconsideration and withdrawal of the rejections.

Rejections under § 112, second paragraph

Claims 40-42, 44, 71 and 78-81 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite.

Claim 40 was rejected as indefinite for omitting essential steps. Without agreeing with the rejection, in the interests of advancing prosecution Applicants have amended claim 40 to include additional steps. Further, amended claim 40 does not recite the following limitations: "the correct conformation" and the "correctly folded nature".

Applicants further amended claim 71 by deleting the limitation "the step" and claim 79, by clarifying which "label-free detection method" is used. Applicants also cancel claims 78 and 81. In view of amendments to claims 40, 71 and 79, and cancellations of claims 78 and 81, Applicants request reconsideration and withdrawal of the rejections.

Rejections under §102(b)

Claims 40-42, 44, and 79 are rejected as anticipated by Bennett et al., Biotechniques 24:478-82, 1998 ("Bennett"). The rejection is traversed to the extent it is applied to the claims as amended.

The present invention relates *inter alia* to a method of detecting protein expression and folding. The instant method enables measuring folding and solubility post-expression ie *in vitro* Specifically, the instant method enables immobilization on a surface, wherein direct detection on surface is achieved and only folded proteins can be immobilized since creation of the antibiotic binding pocket requires a specific folded structure. Further, the instant method enables the percentage of recombinant proteins in its native conformation to be measured.

Claim 40, from which depend the remaining claims subject to the rejection, has been amended to require that the claimed method includes providing a cellular lysate comprising a protein fused to a ble marker protein, and further that the ble fusion protein is immobilized on a surface.

Bennett does not describe a method with these features. Instead, Bennett teaches a cell-based ble fusion protein comprising green fluorescent protein (GFP) and Zeocin™-resistance gene Sh ble for visual screening and selection of transfected mammalian cells. Thus, in Bennett, the binding of Zeocin by the resistance protein is observed indirectly ie it provides resistance to the antibiotic but it is not directly monitored or measured. Although Bennett demonstrates that sufficient protein is expressed to reduce the antibiotic concentration to sub-lethal levels, Bennett is neither able to distinguish native from non-native conformations at a molecular level or a cellular level nor enable specific immobilization of native conformations of the fusion protein.

Bennett, therefore, does not describe the features of the invention now claimed. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Rejections under §103(a)

Claims 71 and 78 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bennett in view of Marcu et al., Journal of the National Cancer Institute 92: 242-48, 2000 ("Marcu"). The rejection is traversed to the extent it is applied to the claims as amended.

The Examiner contends that it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Bennett related to immobilizing the zeocin on a surface, as suggested by the teachings of Marcu, for visualization of the Sh ble-GFP. Applicants respectfully traverse.

Applicants submit that instant claims are non-obvious over the teachings of Bennett and Marcu. Applicants submit that there is no motivation to combine Bennett and Marcu to arrive at the instant invention.

Motivation to combine.

Applicants assert that there is no motivation to combine the teachings of Bennett and Marcu in order to arrive at the instant invention. As is explained by the Federal Circuit, the motivation to combine is part of the discussion in determining the scope and content of the prior art.[1] Thus, where all claim limitations are found in a number of references, the fact finder must determine "[w]hat the prior art teaches... and whether it motivates a combination of teachings from different references".[2].

As detailed above, claims 71 and 78 depend from claim 40. As noted above, claim 40 has been amended so that it is drawn to a method includes providing a cellular lysate comprising a protein fused to a ble marker protein, and further that the ble fusion protein is immobilized on a surface. Bennett describes methods using intact cells. Bennett does not teach or suggest all the elements of the instant claims, including but not limited to providing a cellular lysate comprising a protein fused to a ble marker protein, and further that the ble fusion protein is immobilized on a surface.

Marcu does not remedy the deficiencies of Bennett. Since Hsp90 is a novel molecular drug target, Marcu investigates less toxic agents that are capable of inhibiting Hsp90 function in

[1] DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006); *citing* SIBIA Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356 (Fed. Cir. 2000).

[2] *Id.* citing In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

a manner similar to that seen with the ansamycins and radicicol. Although Marcu discusses Hsp90 binding to antibiotic-coupled beads, Marcu does not suggest that binding of Hsp90 to antibiotic-coupled beads be used as a surrogate for determining the folding/native conformation of a fusion partner.

Thus, one of ordinary skill in the art would not be motivated to look to the teachings of Bennett and Marcu to elucidate the instant method. Applicants request reconsideration and withdrawal of the obviousness rejection.

Claim 80 is rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Bennett in view of Calmels et al., (1993 Molecular Pharmacology 44: 1135-1141) "Calmels". The Examiner contends that it would be obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Bennett by substituting the fluorescently labeled antibiotic of Calmels for the unlabeled antibiotic of Bennett.

As discussed above, Bennett is defective. Calmels does not remedy the deficiencies of Bennett. Calmels describes the subcellular distribution of fluorescently labeled bleomycin and 1:1 stoichiometry of binding to the product of the *Sh ble* gene. Calmels does not teach or suggest an instant method providing a cellular lysate comprising a protein fused to a ble marker protein, and further that the ble fusion protein is immobilized on a surface. Thus, one of ordinary skill in the art would not be motivated to look to the teachings of Bennett and Calmels to elucidate the instant method. Applicants request reconsideration and withdrawal of the obviousness rejection.

CONCLUSION

Favorable action on the merits is respectfully requested. Please contact the undersigned with any questions on the response or application.

If any additional fees are required or if any funds are due, the USPTO is authorized to charge or credit Deposit Account Number: **50-0311**, Customer Number: **35437**, Reference Number: **27353-513 US1**.

Respectfully submitted,

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